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Successful Treatment of Transient Acquired Factor X Deficiency by Plasmapheresis With Concomitant Intravenous Immunoglobulin and Steroid Therapy

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Two patients with no history of previous bleeding diatheses presented with active bleeding from multiple body sites, declining hemoglobin levels, and markedly prolonged prothrombin times (PT) and activated partial thromboplastin times (aPTT) with incomplete correction on PT mix assays. Both patients demonstrated a severe deficiency of factor X (F.X) (<1%; reference range 60–150%). F.X levels and bleeding were refractory to multiple transfusions of fresh frozen plasma (FFP) in both patients. In contrast, daily therapeutic plasma exchange (PLEX) with concomitant administration of intravenous immunoglobulin (IV IgG) and steroids produced a rapid increase in F.X levels with cessation of bleeding, followed by stabilization and normalization of F.X levels and progressive correction of coagulation times. Neither patient has demonstrated a recurrence of the bleeding tendency following discontinuation of steroid therapy. These patients had transient acquired F.X deficiency, a rare coagulopathy, which can result in a lethal bleeding diathesis. An IgG inhibitor that selectively inhibited F.X activation in Russell's viper venom or tissue factor/F.VIIa assays was demonstrated in one patient's pretreatment plasma. Previous treatment of hemorrhage in transient acquired F.X deficiency has been prothrombin complex and/or activated clotting concentrates, which can be associated with transient hypercoagulable states. This is the first reported use of PLEX in transient acquired F.X deficiency. PLEX is safe, efficacious, and rapidly restores hemostasis in this rare acquired bleeding disorder. Am. J. Hematol. 57:245–252, 1998. © 1998 Wiley-Liss, Inc.

Key words: factor X deficiency; plasmapheresis; inhibitor

INTRODUCTION

Isolated factor X (F.X) deficiency may be hereditary (Stuart Prower disease) or an acquired condition. The acquired F.X deficiency states are usually secondary to systemic amyloidosis in which factor X binds irreversibly to amyloid fibrils [1,2]. Transient selective deficiency of F.X with a bleeding diathesis has also been reported in association with some malignancies including one patient with renal and adrenocortical carcinoma [3], five patients with acute myeloid leukemia (two with FAB AML M2, two with FAB AML M3, and one with FAB AML M5 leukemia) [4–6], and one patient with metastatic gastric adenocarcinoma [7]. A separate subset of 11 patients with transient selective F.X deficiency characterized by a marked decrease in F.X activity and a variable bleeding tendency unassociated with systemic amyloidosis or malignancy has been described [8–18]. Presenting signs include massive hematoma or ecchymoses formation [8,9,11,14,15,17], epistaxis [10,13,16], mucocutaneous bleeding [10,16–18], hemarthroses [8,9,17], gross hematuria [8–10,14,16,18], parapharyngeal or mediastinal hemorrhages with airway compromise [15], acute respiratory failure from intrapulmonary hemorrhage [16], and variable gastrointestinal bleeding [9–11,16,17]. There is typically a negative history of bleeding tendency, liver disease, autoimmune disease, or toxin exposure. The prothrombin time (PT) is severely prolonged with variable prolongation of the activated partial

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thromboplastin time (aPTT). F.X activity levels are severely decreased, usually in the range of 1–4%. Attempts to correct this transient F.X deficiency by fresh frozen plasma (FFP) infusions or vitamin K therapy have been unsuccessful. There is no accompanying thrombocytopenia.

Etiologic factors associated with transient acquired F.X deficiency include a preceding acute viral respiratory infection or pneumonia [11–16], and single case reports of mycoplasma infection [10] or fungicide exposure [8]. The pathogenesis and transient nature of the disorder remain incompletely understood. The transient deficiency of F.X does not appear to be secondary to inadequate synthesis, and factors II, VII, and IX are typically only mildly or moderately reduced. No inhibitor has been demonstrable in the majority of the previously reported cases [8–15]. However, evidence of a specific F.X inhibitor has been demonstrated in the three most recently described patients [16–18].

We now report two additional patients with transient acquired F.X deficiency and describe the first use of therapeutic plasma exchange (PLEX) with concomitant IV IgG and steroid therapy to successfully correct the severe bleeding tendency associated with this disorder. An IgG inhibitor that selectively inhibits F.X activation by tissue factor/F.VIIa or Russell's viper venom was found in one of these patients providing additional insights into the pathogenesis of this rare acquired coagulopathy.

MATERIALS AND METHODS

Therapeutic Plasma Exchange (PLEX)

Daily PLEX was performed in both patients using a Cobe Spectra (Englewood, Colorado). Approximately one plasma volume (3.6–5.0 L) was exchanged during each PLEX procedure. In patient R.K., the first PLEX procedure utilized 100% fresh frozen plasma (FFP) as replacement fluid. In the subsequent 3 procedures performed on patient R.K., the first 2,000 ml were replaced with albumin followed by FFP replacement. The use of albumin replacement was necessitated by the uncommon plasma type of patient R.K. (AB) and limited FFP availability. A total of 37 FFP units was administered to patient R.K. via PLEX. In patient R.E., daily PLEX employed 100% FFP as replacement fluid. A total of 23 FFP units were administered to patient R.E. by PLEX.

Russell's Viper Venom Test (RVVT)

The active principle purified from the crude venom of *Vipera russelli* may be used to activate F.X directly, in the absence of other coagulation factors. A dilute Russell's viper venom (RVV) test was employed to demonstrate the specific inhibition of F.Xa generation by the patient's platelet-poor plasma (PPP). Serial dilutions of patient PPP were added to 1:20 diluted reference human PPP in a microtiter plate followed by addition of 2 mM RVV with 2 mM Spectrozyme F.Xa (American Diagnostica, Greenwich, CT). The absorbance (405 nm) of the test mixtures was measured kinetically (Vmax; Molecular Devices, Palo Alto, CA) for 30 min.

Tissue Factor/Factor VIIa Complex (TF/F.VIIa) Assay

Tissue factor complexes with F.VII to form a TF/F.VIIa complex capable of direct F.X activation. A TF/F.VIIa assay was employed to demonstrate the specific inhibition of F.Xa generation by the patient's PPP. Serial dilutions of patient PPP were added to 1:20 diluted reference human PPP in a microtiter plate followed by addition of 1 nM F.VIIa, diluted human brain tissue factor (purified in our laboratory), and 2 mM Spectrozyme F.Xa. The absorbance (405 nM) of the test mixtures was measured kinetically for 20 min.

Anti-Factor X Antibody Isolation

Patient PPP (1.5 ml) obtained prior to transfusion or treatment by PLEX, and which had been previously shown to specifically inhibit TF/F.VIIa activation of reference human PPP, was doubly precipitated with 0.750 ml of saturated ammonium sulfate, pH 7.4. The precipitates, containing mostly IgG, were combined and resuspended in 0.500 ml phosphate buffered saline (PBS), pH 7.4, then dialyzed in 50.0 ml PBS for 3 hr with 6 changes of buffer. Serial dilutions of the patient PPP precipitate were tested for specific inhibition of F.X activation in the RVVT vs. a reference human PPP precipitate.

CASE HISTORIES AND RESULTS

Patient R.K.

A 41-year-old Caucasian man, employed as a commercial sandblaster and painter, was in his usual state of excellent health until approximately 1 week prior to admission when he experienced transient chest pain associated with the use of a new paint formulation. He subsequently developed painless hematuria followed by progressively worsening abdominal and back pain. The patient denied previous viral symptoms or history of previous bleeding tendency. The patient developed an expanding hemorrhage within the soft tissues of the jaw and inferolingual region. He was transferred to the University of North Carolina Hospitals with continuing massive hematuria, a coagulopathy of unknown etiology, syncopal symptoms, decreasing renal function, and a parapharyngeal hematoma that threatened to compromise his airway.

Admission laboratory studies are shown in Table I. The patient exhibited markedly prolonged PT and aPTT. PT mixture assay demonstrated an incomplete correction

TABLE I. Admission Laboratory Profiles of Patients R.K. and R.E.

Laboratory test	Patient R.K.	Reference range	Patient R.E.	Reference range
Coagulation studies				
Prothrombin time	>60 sec	10.0–12.4 sec	>60 sec	10.6–14.0 sec
Activated partial thromboplastin time	83.3 sec	21.5–31.9 sec	91.6 sec	27.6–34.8 sec
Thrombin clot time	11.1 sec	9.8–14.0 sec	12.9 sec	9.8–14.0 sec
PT mix	16.2 sec	10.0–12.4 sec	15 sec	10.6–14.0 sec
aPTT mix	31.8 sec	21.5–31.9 sec	32.3 sec	27.6–34.8 sec
Fibrinogen	416 mg/dL	152–367 mg/dL	438 mg/dL	142–474 mg/dL
Factor II	54%	60–150%	76%	60–150%
Factor V	98%	60–150%	88%	60–150%
Factor VII	35%	60–150%	45%	60–150%
Factor VIII	238%	60–150%	219%	60–150%
Factor IX			86%	60–150%
Factor X	<1%	60–150%	<1%	60–150%
Protein C activity	79%	58–201%		
Hematologic studies				
White cell count	10.9×10^9/L	$4–12 \times 10^9$/L	12.7×10^9/L	$4–12 \times 10^9$/L
Hemoglobin	6.4 g/dL	13.4–17.4 g/dL	7.6 g/dL	12.3–15.7 g/dL
Hematocrit	18%	40–54%	22%	38–47%
Platelet count	202×10^9/L	$150–440 \times 10^9$/L	442×10^9/L	$150–440 \times 10^9$/L
Chemistry studies				
Blood urea nitrogen	31 mg/dL	8–20 mg/dL	49 mg/dL	8–20 mg/dL
Serum creatinine	3.9 mg/dL	0.8–1.5 mg/dL	1.2 mg/dL	0.6–1.2 mg/dL

suggestive of a possible inhibitor. An aPTT mixture assay was within the reference interval. Specific factor assays revealed mildly decreased factor II (54%) and factor VII (35%) and profoundly decreased factor X (<1%). Serum warfarin was <0.1 mcg/ml. There was no evidence of liver dysfunction. Tests for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C were negative. Vitamin K was given subcutaneously at 20 mg/day X 3 without apparent effect. Continued severe bleeding was treated with multiple transfusions of 22 U FFP and 11 U packed red blood cells (pRBCs). Large volume FFP transfusion during the initial hours of hospitalization negligibly raised F.X levels (<1 to 2%), without apparent beneficial effect on the patient's bleeding diathesis. Acute respiratory distress followed the development of new parapharyngeal hematomas and required an emergent tracheostomy to avert airway compromise.

The failure of multiple repeated transfusions of FFP and pRBCs to correct for the coagulopathy implied that an inhibitor might be present, despite the partial normalization of assay times on PT and aPTT mix tests. A decision was made to attempt plasmapheresis in this patient with ongoing renal and pulmonary bleeding, fluid overload, acute renal failure, and severe respiratory impairment within hours of his admission. Daily therapeutic plasma exchange (PLEX) for four consecutive days with albumin and FFP replacement was performed. PLEX was started simultaneously with administration of IV IgG and steroids. IV IgG was administered 1 g/kg/day × 2 days. IV IgG was repeated once at an equivalent dose later in the hospital course (Fig. 1). Steroid therapy was comprised of methylprednisolone 500 mg IV qday × 3 days, then 60 mg IV q8 hr × 3 days followed by prednisone 60 mg PO with a slow taper.

One hundred percent FFP was used for replacement during the initial PLEX procedure. This effectively restored hemostatic integrity and removed some of the excess intravascular volume from this massively transfused patient. A rapid elevation of F.X levels from ~2 to 25% occurred with PLEX and was accompanied by cessation of significant bleeding and rapid correction of PT and aPTT (Fig. 1). The subsequent three PLEX procedures used albumin as replacement for the initial 2.0 L and then FFP for replacement fluid with a total replacement volume of 4.0–4.5 L. One hundred percent FFP was not used due to the uncommon blood type of the patient (AB) and an acute scarcity of AB plasma. F.X levels following subsequent daily PLEX procedures remained elevated within a range of 29–40% and PT and aPTT showed progressive correction.

After discontinuation of daily PLEX, there was a transient mild decrease in F.X levels and a transient moderate prolongation of the PT (Fig. 1). The remainder of the hospital course was notable for progressive correction of coagulation times, normalization of F.X levels, rapid recovery from ARF, and progressive improvement in respiratory status. At discharge (hospital day 13; 326 hr), the patient had a F.X level of 92%, PT of 11.4 sec, and aPTT of 26.9 sec. The patient was discharged to home on hospital day 16 with tapering steroid therapy. Three days

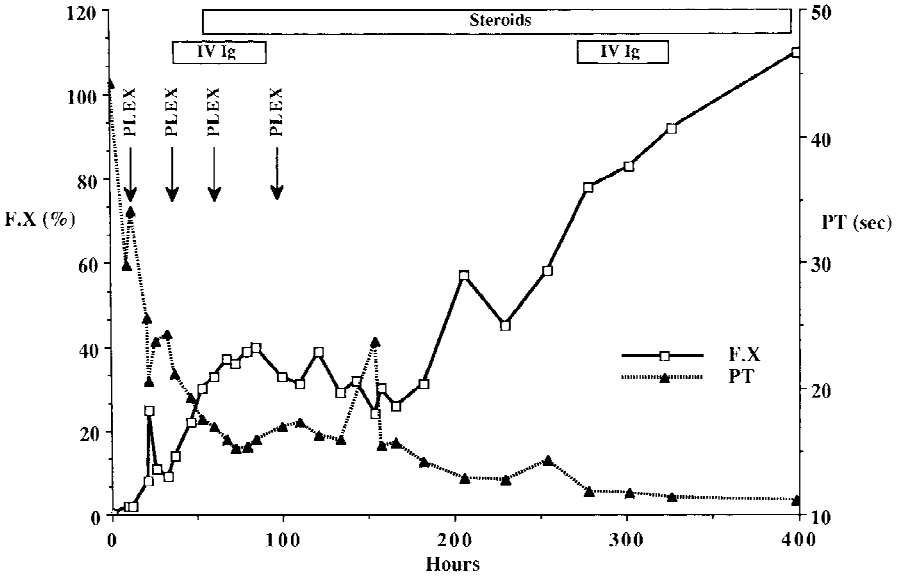

Fig. 1. Clinical course of patient R.K. Therapeutic plasma exchange (PLEX) was performed at 20, 49, 66, and 91 hr after admission using albumin and fresh frozen plasma as replacement fluids. IV IgG and steroids were administered concomitantly with PLEX. A rapid elevation of factor X (F.X) occurred immediately following PLEX with maintenance of activity within acceptable ranges for hemostatic integrity. A spontaneous recovery of F.X activity later occurred with return to normal activity levels. A rapid and progressive correction of prothrombin time (PT) accompanied daily PLEX.

after discharge (398 hr) the patient had a F.X level of 110%, PT of 11.2 sec, and aPTT of 23.9 sec. No recurrence of abnormal bleeding has arisen following discontinuation of steroid therapy (follow up interval 5 months).

Patient R.E.

A 77-year-old Caucasian woman was admitted to an outside hospital with a 2-day history of epistaxis and generalized bruising without associated trauma. The patient had no history of menorrhagia, postpartum bleeding, or gingival bleeding. She denied warfarin usage, toxin or pesticide exposure. She reported a preceding viral syndrome characterized by nausea and upper respiratory symptoms beginning approximately 2 weeks PTA. She was initially treated with 3 U FFP, 2 U pRBCs, and Vitamin K 10 mg SQ. She continued to experience epistaxis and developed guaiac positive stools and gross hematuria. She was transferred to UNC Hospitals with a diagnosis of paraproteinemia vs. an acquired coagulation pathway defect.

Admission laboratory studies are shown in Table I. The patient was noted to have extensive ecchymoses involving all extremities and the gluteal regions as well as the periorbital soft tissues. She also demonstrated a right conjunctival hemorrhage, continued epistaxis, hemorrhage in the floor of the mouth and left buccal mucosa, melena, and gross hematuria. Initial laboratory studies showed a markedly prolonged PT and aPTT. PT mixture assay demonstrated an incomplete correction suggestive of a possible inhibitor. An aPTT mixture assay was within the reference interval. Specific factor assays revealed mildly decreased factor VII (45%) and profoundly decreased factor X (<1%). Serum protein electrophoresis was within normal limits. A bone marrow aspiration showed sideroblastic anemia, and no evidence of myeloma or amyloidosis. The patient was diagnosed with acquired F.X deficiency secondary to viral illness and was started on daily PLEX with FFP exchange for 2 days with concomitant IV IgG and steroid therapy. IV IgG was administered 1 g/kg/day × 2 days. Steroid therapy was methylprednisolone 40 mg IV q 6 hr × 2 days, then 20 mg IV q 6 hr × 1 day, then 20 mg IV q 8 hr × 1 day, then 20 mg IV q 12 hr × 1 day, followed by prednisone 20 mg PO BID with a slow taper.

One hundred percent FFP was used for replacement during PLEX with a total replacement volume of 3.6–3.8 L. A rapid elevation of F.X occurred immediately following initiation of PLEX (Fig. 2). F.X levels were increased from 1 to 21% by the first PLEX, and from 4 to 42% by the second PLEX. F.X levels fell precipitously in the hours following the PLEX procedures; however, F.X was maintained at a minimum of 13% by the second day of admission without additional FFP transfusion. The patient exhibited progressive improvement with only minimal residual hematuria. Complete cessation of bleeding occurred simultaneously with a rapid and spontaneous recovery of F.X during hospital days 3 and 4 (Fig. 2). PLEX was also accompanied by a rapid correction of PT and aPTT (Fig. 2). F.X levels as well as PT and aPTT demonstrated progressive corrective trends during the remainder of the hospitalization. At discharge (hospital day 7; 185 hr), the patient exhibited F.X 81%, PT 12.6 sec, and aPTT 23.3 sec. The patient was discharged to home with tapering steroid therapy.

Demonstration of F.X Activation Inhibitor

A dilute Russell's viper venom test (RVVT) was performed on platelet-poor plasma (PPP) from patient R.K. obtained prior to PLEX or FFP transfusions and was

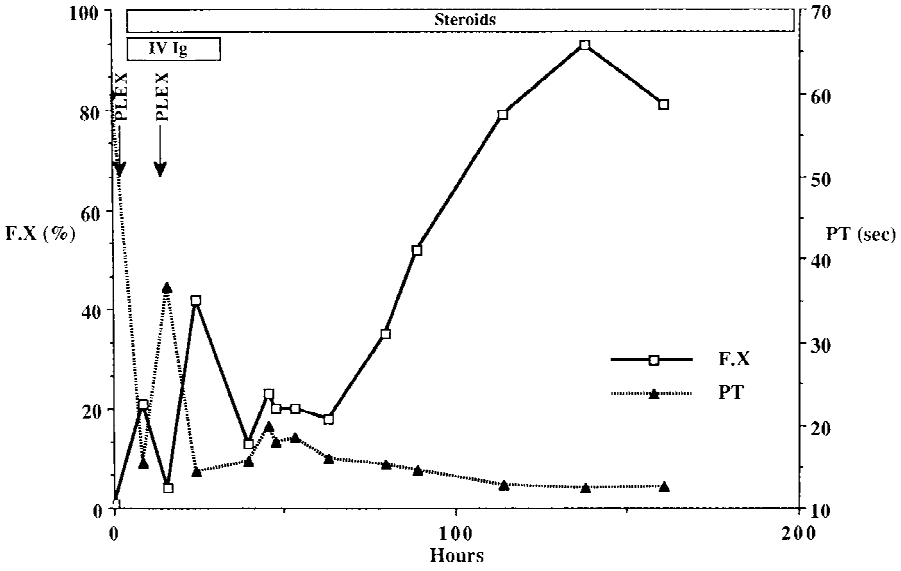

Fig. 2. Clinical course patient R.E. Therapeutic plasma exchange (PLEX) was performed at 7 and 24 hr after admission using fresh frozen plasma as replacement fluid. IV IgG and steroids were administered concomitantly with PLEX. A rapid elevation of factor X (F.X) occurred immediately following PLEX with maintenance of activity within acceptable ranges for hemostatic integrity. A spontaneous recovery of F.X activity later occurred with return to normal activity levels. A rapid and progressive correction of prothrombin time (PT) accompanied daily PLEX.

noted to be abnormal compared to control F.X deficient plasma. The RVVT time was markedly prolonged by the addition of patient PPP. Interestingly, a specific F.X assay was not inhibitory, characteristic of this transient coagulopathy. Further testing of serially diluted patient PPP revealed specific inhibition of the effects of Russell's viper venom (Fig. 3A) and TF/F.VIIa (Fig. 3B) on 1:20 reference human PPP. The progressive decrease in absorbance at increasing patient PPP concentrations corresponds to decreasing F.Xa generation in both the RVVT and TF/F.VIIa systems. The inhibitory effect of the patient PPP was concentration dependent. Similarly, the effect of diluted patient PPP on peak F.Xa generation was assessed using the RVVT (Fig. 4A) and TF/F.VIIa assays (Fig. 4B). The patient PPP inhibited F.Xa generation in a concentration-dependent fashion. Serial dilutions of the antibody prepared by double precipitation of the patient PPP also caused specific inhibition of Russell's viper venom activation of F.X in reference PPP. In contrast, the precipitate prepared from reference PPP revealed no inhibition of factor X activation (data not shown).

DISCUSSION AND CONCLUSIONS

Transient acquired F.X deficiency is an uncommon self-limited disorder characterized by a marked decrease in F.X activity and a variable bleeding tendency. Although the disorder was first recognized at the University of North Carolina in 1956 and reported in 1959 [8], the pathogenesis and transient nature of the disorder remain poorly understood. It has been suggested that patients with acquired transient F.X deficiency have a selective abnormal clearance of F.X [10,14]. Circulating endogenous inhibitors to F.X are generally not identified. However, there is a report of a circulating inhibitor in an elderly woman with transient selective deficiency of F.X, which demonstrated inhibition of F.X and F.Xa activities in a Russell's viper venom assay [16]. There is additionally a report of a transient IgG F.X inhibitor producing multiple cutaneous and gastrointestinal hemorrhages in an elderly woman with transient selective deficiency of F.X [17]. This inhibitor also showed a markedly abnormal Russell's viper venom time [17]. Most recently, a patient was identified with transient acquired F.X deficiency associated with an IgG, which bound to the light chain of intact F.X and inhibited activation of F.X by TF/F.VIIa, F.IXa/F.VIIIa/phospholipid complex, or Russell's viper venom [18].

We now report identification of a circulating antibody in a patient with transient acquired F.X deficiency, which specifically inhibits F.Xa generation in both Russell's viper venom and TF/F.VIIa assays. The development of this IgG inhibitor resulted in a self-limited episode of life-threatening bleeding in an otherwise healthy adult man. The etiology of this inhibitor remains obscure. No viral prodrome or upper respiratory tract infection was noted in this patient, unlike most others with this transient coagulopathy. We concur with the suggestion of Rao et al. [18] that laboratory evaluation of patients with transient acquired F.X deficiency should include evaluation for F.X inhibitors by RVVT and/or TF/F.VIIa assays to identify inhibitors that may not be demonstrable by standard methods.

The correction of the bleeding diathesis in transient acquired F.X deficiency has been difficult in reported cases. The use of FFP typically produces no change in PT, F.X levels or clinical status unless extremely large volumes are used. Prednisone therapy has been used with unclear effects given the self-limited nature of the disorder [11,18]. Attempted treatment of patients with acquired F.X deficiency and life-threatening hemorrhage

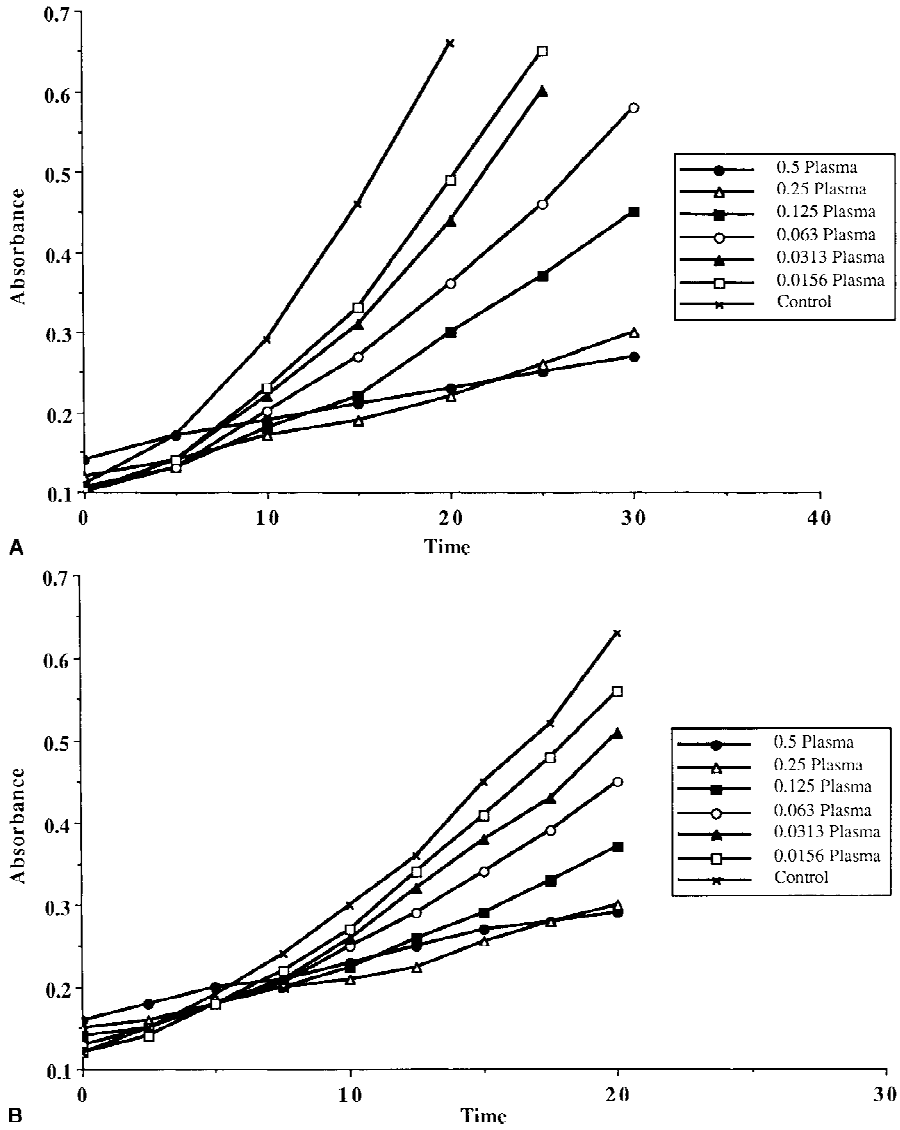

Fig. 3. Inhibition of Russell's viper venom and tissue factor/factor VIIa assay by patient R.K. plasma. Serial dilutions of patient platelet-poor plasma (PPP) were added to 1:20 diluted reference human PPP in a microtiter plate followed by addition of 2 nM Russell's viper venom with 2 mM Spectrozyme F.Xa. The absorbance (405 nm) of the test mixtures was measured kinetically over time. A: Serially diluted patient PPP inhibits the action of Russell's viper venom. The "control" test mixture contains only diluent in place of the patient PPP. B: Serially diluted patient PPP inhibits the action of the TF/F.VIIa complex in reference human PPP in a concentration dependent fashion. The "control" test mixture contains only diluent in place of the patient PPP.

has most recently used prothrombin complex (Konyne) [11] and/or activated clotting concentrates (Autoplex T) [15]. The use of prothrombin complex alone produces a brief correction of PT and elevation of F.X without effective hemostasis [11]. Although the use of activated clotting complex (Autoplex T) has resulted in the correction of prothrombin time and clinical resolution of bleeding in a patient with transient F.X deficiency, a transient hypercoagulable state with multiple cerebral infarctions was seen in one case [15]. Therapy using prothrombin complex concentrates to correct bleeding secondary to F.IX or F.X deficiency or F.VIII inhibitors can be hazardous and has been associated with significant patient morbidity and mortality. The use of prothrombin complex concentrates in the treatment of F.IX deficiency or F.VIII inhibitors has been associated with a risk of potentially fatal bleeding or thromboembolic complications including acute myocardial infarction [19,20] and disseminated intravascular coagulation [20]. The administration of prothrombin complex concentrate to a patient with hereditary severe F.X deficiency has resulted in fatal diffuse thromboembolism [21].

We report that plasmapheresis with concomitant administration of IV IgG and steroids has been used to achieve rapid and sustained correction of F.X levels, PT, and aPTT in two patients with transient acquired F.X deficiency. Although the use of plasma for replacement therapy in plasmapheresis has a small risk of disease transmission and of allergic or anaphylaxis, overall, we feel this therapeutic approach is safe and efficacious, producing rapid cessation of bleeding. The strong corrective response in F.X levels following completion of plasmapheresis supports the presumed immune etiology of this acquired coagulopathy. The possible risks of prothrombin complex administration are avoided by this therapeutic approach. Although plasmapheresis has been

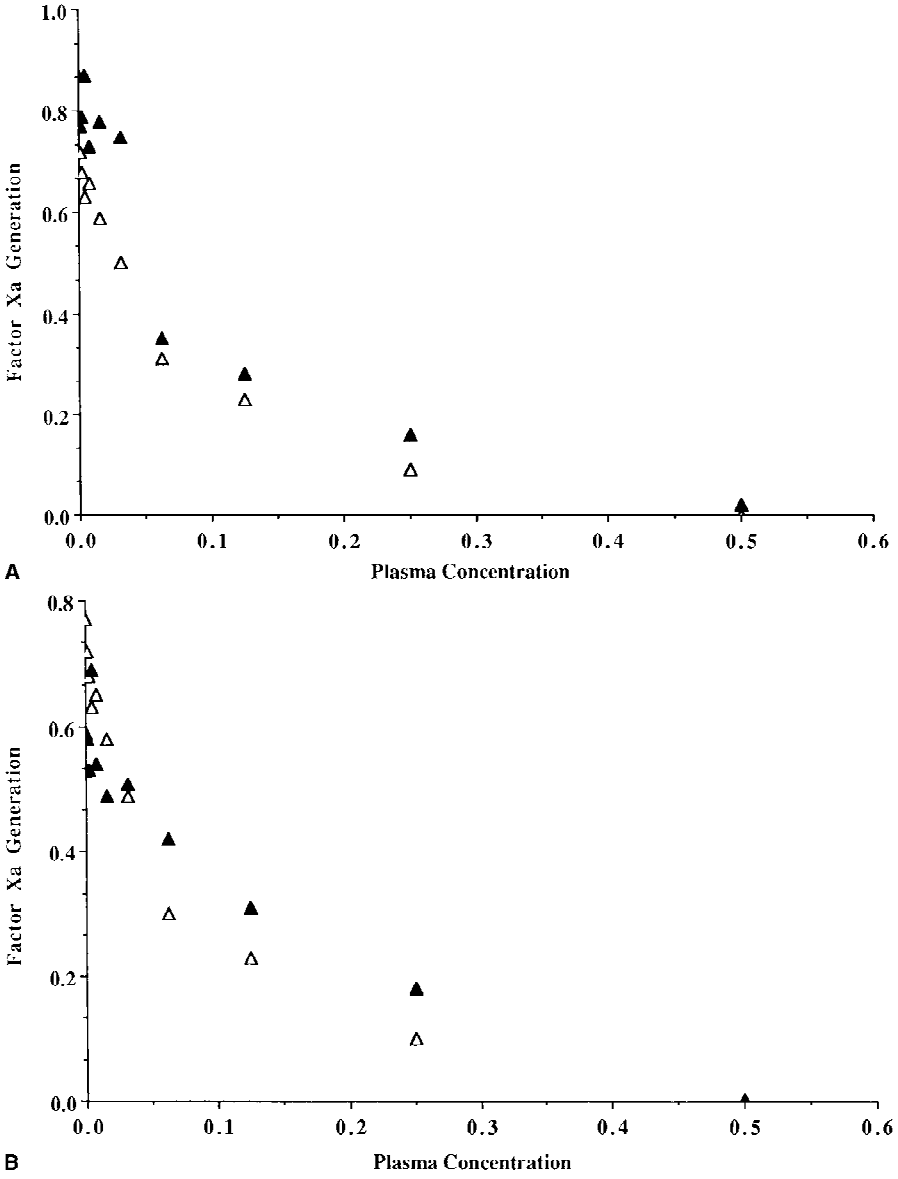

Fig. 4. Effect of patient R.K. plasma on factor Xa generation in Russell's viper venom test and tissue factor/ factor VIIa assay. A: Serial dilutions of patient platelet-poor plasma (PPP) were added to 1:20 diluted reference human PPP in a microtiter plate followed by addition of 2 nM Russell's viper venom with 2 mM Spectrozyme F.Xa. Peak F.Xa generation is displayed for each dilution of patient PPP. The patient PPP inhibited F.Xa generation in a concentration dependent fashion. B: Serial dilutions of patient PPP were added to 1:20 diluted reference human PPP in a microtiter plate followed by addition of 1 nM F.VIIa, diluted human brain tissue factor, and 2 mM Spectrozyme F.Xa. Peak F.Xa generation is displayed for each dilution of patient PPP. The patient PPP inhibited F.Xa generation in a concentration dependent fashion.

used in the treatment of acquired inhibitors in the setting of hemophilia, this approach has been less than optimally effective. We propose that plasmapheresis with accompanying IV IgG and steroid therapy should be the treatment of choice in patients with transient acquired F.X deficiency and considered a safe therapeutic alternative to activated clotting concentrates.

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